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788,301



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COMPLETE SPECIFICATION

A Process for the Manufacture of 6,10-Dimethyl-Undecanone-(2)

We, F. HOFFMANN-LA ROCHE & Co., Aktiengesellschaft, a Swiss Company, of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to the synthesis of 6,10-dimethyl-undecanone-(2) [otherwise known as hexahydro-pseudoionone]; more particularly, the invention is concerned with a process for the manufacture of said compound from 6,10-dimethylundecadien-(5,9)-one-(2) [otherwise known as geranyl-acetone] or 6,10-dimethyl-undecen-(5)-one-(2) [otherwise known as tetrahydro-pseudoionone] and with a synthesis of said compound incorporating said process.

Hexahydro-pseudoionone is useful for the manufacture of isophytol which, in turn, is useful for the manufacture of vitamin E and vitamin K. It is a known compound. Hitherto it has been prepared from citral and other natural products by a process which was attended by considerable difficulty arising out of the contamination of the product with substances formed as by-products in the process. The hexahydro-pseudoionone provided by the process of this invention, to be described hereinafter, is in a purer form than that obtained by processes hitherto used.

According to the process provided by the

invention hexahydro-pseudoionone is manufactured by the catalytic hydrogenation of geranyl-acetone or tetrahydro-pseudoionone. The hydrogenation is preferably carried out in the presence of a palladium catalyst. However, any hydrogenation catalyst which does not lead to the addition of hydrogen at the carbonyl group can be used. The use of an inert solvent or the application of heat is not necessary. According to whether geranyl-acetone or tetrahydro-pseudoionone is used, two mols or one mole of hydrogen are or is taken up during the process.

The synthesis of hexahydro-pseudoionone incorporating the aforesaid process and also provided by the invention utilizes 6-methylhepten-(5)-one-(2) or 6-methyl-heptanone-(2) as initial materials. It comprises adding the elements of acetylene to either of these materials by treating same with an alkali-metal derivative of acetylene in liquid ammonia solution and treating the product with a non-alkaline hydrolysing agent, partially hydrogenating the triple bond in the resulting acetylenic carbinol so as to convert said bond into a double bond, reacting the partial-hydrogenation product with diketene, eliminating the elements of carbon dioxide from the reaction product by heating same and catalytically hydrogenating the geranyl-acetone or tetrahydro-pseudoionone so obtained.

The synthesis may be illustrated thus:—

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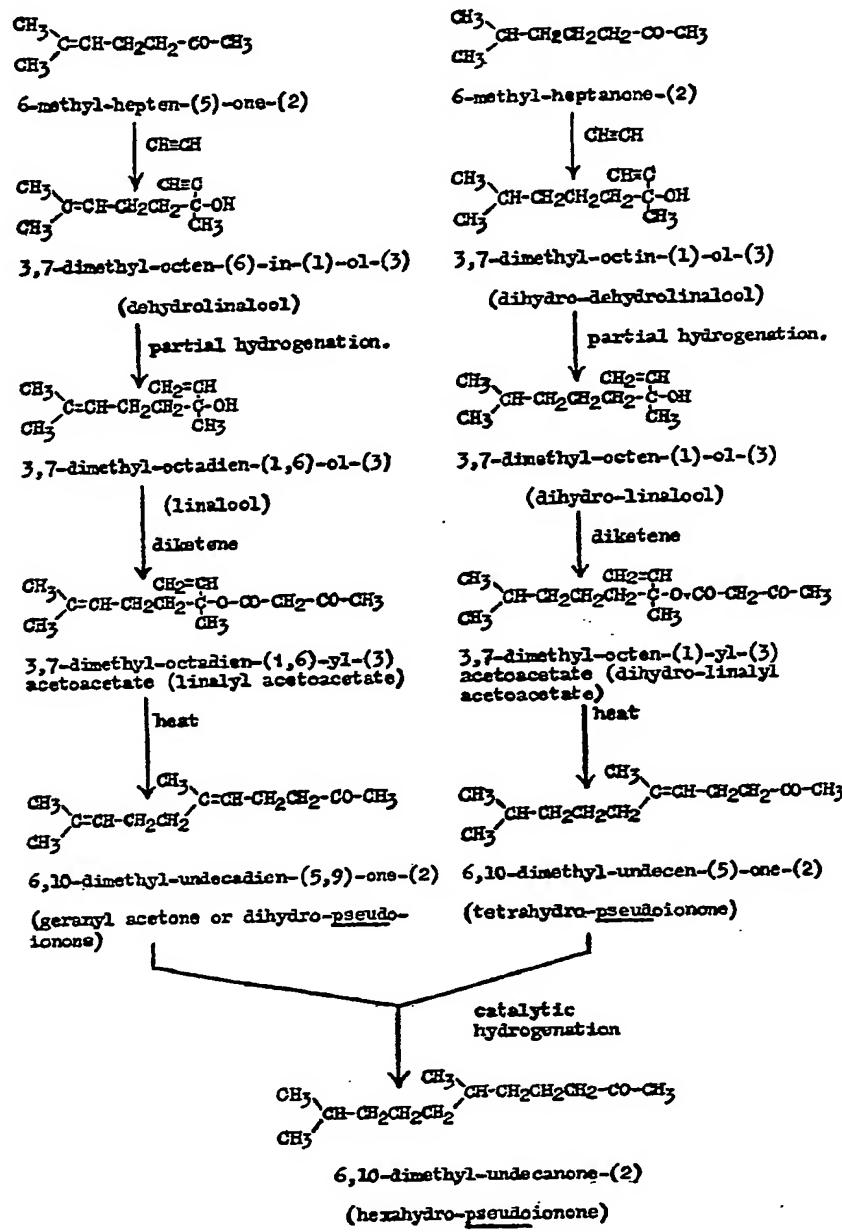
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5 A further synthesis embodying the step of catalytically hydrogenating geranyl-acetone or tetrahydro-pseudoionone is described and claimed in the specification of our copending application for Letters Patent No. 4877/56 (now serial no. 788,302).

10 The addition of the elements of acetylene to the 6-methyl-hepten-(5)-one-(2) or to the 6-methyl-heptanone-(2) may be carried out by treating either compound in liquid ammonia solution with an alkali-metal derivative of acetylene and treating the product with a dilute aqueous acid, with water or with non-alkaline ammonium salts as such or aqueous

solutions thereof. The alkali-metal derivative may be made by passing acetylene into a solution of the alkali-metal (e.g. sodium) or alkali-metal amide (e.g. sodamide) in liquid ammonia. In this way an acetylene-carbinol (that is to say, dehydrolinalool or dihydro-dehydrolinalool) is obtained in an almost quantitative yield.

15 The partial hydrogenation of the triple bond of the acetylene-carbinol aforesaid is carried out by catalytic hydrogenation in the presence of a selective palladium- or nickel-catalyst. For example, an almost quantitative yield is obtained by hydrogenation with a

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5 palladium/calcium-carbonate catalyst which has been deactivated by means of lead. This step leads to the formation of a vinyl-carbinol (that is to say, linalool or dihydro-linalool).

10 The reaction of the partial-hydrogenation product with diketene is best carried out by the gradual addition of diketene to the said vinyl-carbinol in the presence of a weakly acid agent, e.g. a mixture of pyridine and acetic acid or of choline and acetic acid. The reaction can be carried out with or without a solvent. The resulting acetoacetate compound (that is, linalool acetoacetate or dihydro-linalool acetoacetate) need not be isolated or purified for the next step.

15 The elements of carbon dioxide are eliminated from the aforesaid acetoacetate compound by application of heat. The elimination is accompanied by an internal rearrangement. A high temperature, preferably between 140°—180° C., is required. The product of this step is geranyl acetone or tetrahydro-*pseudoionone* and may be hydrogenated to give hexahydro-*pseudoionone* in the manner indicated hereinbefore.

20 The hexahydro-*pseudoionone* produced in accordance with the invention is very pure. The reagents used in the synthesis are easily and economically obtainable and the various steps give almost quantitative yields. The new process provides an advantageous and total synthesis of hexahydro-*pseudoionone* which is purer than that hitherto obtained from citral and other natural products.

25 The dihydro-linalyl acetoacetate obtained in the foregoing process by the action of diketene on dihydro-linalool is a new substance. It is claimed *per se* in the specification of Application for Letters Patent No. 29,635/56 (now serial No. 788,303). Also claimed in said specification is the three-step process for the manufacture thereof described earlier herein [that is, the addition of acetylene to 6-methyl-heptanone-(2) followed by partial hydrogenation and reaction with diketene].

30 The following examples are illustrative of the said process and said synthesis:—

EXAMPLE 1.

a) Dehydro-linalool.

35 Sodium acetylide was prepared in a 3-litre 3-neck flask equipped with stirrer, dropping funnel, gas inlet tube and dry-ice reflux condenser, by bubbling acetylene into a solution of 57.5 g. (2.5 mols) of sodium dissolved in 800 ml. of liquid ammonia. Completion of this reaction was signified by disappearance of the blue colour.

40 To the mixture was added, dropwise during two hours, a solution of 302.2 g. (2.4 mols) of 6-methyl-hepten-(5)-one-(2) in 300 ml. of toluene. A slow stream of acetylene was continued during this time, and for an additional hour. The reaction was allowed to continue for eighteen hours, and then the ammonia

45 was distilled off in a stream of nitrogen. Finally, the reaction mixture was poured carefully onto a mixture of 200 g. of sulphuric acid and 800 g. of ice, maintained at 10°—20° C. by external cooling. The organic layer was separated, and washed with saturated sodium bicarbonate solution, and then with water until neutral. After removal of the solvent *in vacuo*, distillation of the residue afforded 346.5 g. (95 per cent. of 3,7-dimethyl-octen-(6)-yne-(1)-ol-(3) [dehydro-linalool]; b.p. 88°—90° C./14 mm., $n_{D}^{25} = 1.4608$.

b) Linalool.

50 A solution of 465 g. (3.0 mols) of the 3,7-dimethyl-octen-(6)-yne-(1)-ol-(3) in 900 ml. of petroleum ether (60° C.) was hydrogenated at 10° C., at atmospheric pressure, in the presence of 23 g. of a lead-poisoned 5 per cent. palladium/calcium-carbonate catalyst [LIND-LAR, Helvetica Chimica Acta, 1952, 35, 446]. Exactly 3 mols of hydrogen were consumed in four hours, when the absorption of hydrogen had virtually ceased. The catalyst was removed by filtration and after removal of the solvent *in vacuo*, the product was distilled at reduced pressure. 3,7-dimethyl-octadien-(1,6)-ol-(3) [linalool] was collected at 82° C./10 mm. $n_{D}^{25} = 1.4590$; yield, 439 g. (95 per cent.).

c) Linalyl acetoacetate.

55 A 3-litre 3-neck flask equipped with stirrer, thermometer, dropping funnel and condenser protected by calcium chloride tubes, was charged with 771 g. (5.0 mols) of the 3,7-dimethyl-octadien-(1,6)-ol-(3), 770 ml. of toluene, 15 ml. of pyridine and 15 ml. of acetic acid. To this solution were added, dropwise, during three hours, 445.7 g. (5.3 mols) of diketene. An exothermic reaction ensued, and the reaction temperature was maintained at 25°—30° C. by external cooling. Stirring was continued for an additional four hours, when there was no further heat evolution.

60 The reaction mixture was washed successively with water, 1 N hydrochloric acid, water, saturated sodium bicarbonate, and finally with water until neutral. The organic layer was concentrated *in vacuo*, leaving crude 3,7-dimethyl-octadien-(1,6)-yl-(3) acetoacetate [linalyl acetoacetate] as a yellow-orange oil, in quantitative yield; $n_{D}^{25} = 1.4638$. This crude product is of sufficient purity for use in the next step.

d) Dihydro-*pseudoionone*

65 A 3-litre 3-neck flask equipped with a stirrer, thermometer and reflux condenser, the top of which was connected through a dry-ice trap to a gas meter, was charged with 1192 g. (5.0 mols) of the crude 3,7-dimethyl-octadien-(1,6)-yl-(3) acetoacetate. The flask was heated by an oil-bath to 140°—150° C., whereby carbon dioxide was evolved rapidly. After two hours, the rate of gas evolution had

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diminished considerably, so the reaction temperature was increased to 155°—165° C. The reaction was terminated after five hours, when the production of carbon dioxide was 90 per cent. of theory. By fractional distillation of the reaction mixture from an efficient column, there were collected 754 g. (77.5 per cent.) of 6,10-dimethyl-undecadien-(5,9)-one-(2) [dihydro-pseudoionone or geranyl acetone], b.p. 82°—83° C. (0.8 mm.); $n_{D}^{25} = 1.4658$.

e) Hexahydro-pseudoionone

A stirring autoclave was charged with 2,000 g. of the 6,10-dimethyl-undecadien-(5,9)-one-(2) and with 100 g. of 5 per cent. Lindlar lead-palladium/calcium-carbonate catalyst. Hydrogen was introduced under a pressure of 500 lbs per square inch. Stirring was started, while cooling the autoclave, and the temperature was allowed to rise to a maximum of about 95° C. within about thirty minutes. The cooling was then ended and heat was supplied to the autoclave, and the reaction was continued for an additional period of approximately ninety minutes at about 95°—100° C. At the end of this time, the contents of the autoclave were removed and filtered. The filtrate consisted essentially of 6,10-dimethyl-undecanone-(2) [hexahydro-pseudoionone], a clear colourless liquid of somewhat musty odour, b.p. 63°—65° C./0.3 mm. $n_{D}^{25} = 1.4325$.

EXAMPLE 2.

a) Dihydro-dehydrolinalool.

To 7 litres of liquid ammonia, there were added 193 g. of metallic sodium over a period of one hour. Acetylene gas was then bubbled into the reaction until the solution changed colour from a dark blue to white. 896 g. of 6-methyl-heptanone-(2), dissolved in an equal volume of diethyl ether, were then dropped in while stirring in one hour. The acetylene addition was continued for an additional three hours. The reaction was stirred all night, then the ammonia was distilled off with the aid of nitrogen gas. The residue was washed with 5 per cent. sulphuric acid, then until neutral with water. On fractionation, the product, 3,7-dimethyl-octin-(1)-ol-(3) [dihydro-dehydrolinalool], distilled at 132° C. (150 mm.) $n_{D}^{25} = 1.4380$. The yield was 82.2 per cent. of theory.

b) Dihydro-linalool.

308 g. of the 3,7-dimethyl-octin-(1)-ol-(3) were placed in a 3-litre flask provided with a mercury sealed stirrer. To this there were added 20 g. of Lindlar lead-palladium/calcium-carbonate catalyst and 500 ml. of petroleum ether. The hydrogenation was carried out at ca 20° C., which went quite rapidly until two mols of hydrogen were consumed. Six hours were required for the reduction to be completed. The catalyst was filtered off and the product was fractionated *in vacuo*. There were obtained 249.5 g. of 3,7-dimethyl-octen-(1)-ol-(3) [dihydro-linalool] distilling at 81° C.

(10 mm.), $n_{D}^{25} = 1.4345$ —1.4350. The yield was 80 per cent. of theory.

c) Dihydro-linalyl acetoacetate.

Into a 2-litre 3-neck flask equipped with a stirrer, thermometer, dropping funnel and condenser, there were placed 234.4 g. (1.5 mols) of the 3,7-dimethyl-octen-(1)-ol-(3), 234 ml. of petroleum ether (30° C.), 3 ml. of pyridine and 3 ml. of acetic acid. To the mixture were added, dropwise, during two hours 138.8 g. (1.65 mols) of diketene, while maintaining a temperature of 25°—30° C. by external cooling. Stirring was continued for an additional six hours at that temperature. Then, the solution was washed successively with 200 ml. of water, twice with 200 ml. of 10 per cent sulphuric acid, again with 200 ml. of water, three times with 200 ml. of saturated sodium bicarbonate, and finally with water until neutral. The organic layer was concentrated *in vacuo*, leaving crude 3,7-dimethyl-octen-(1)-yl-(3) acetoacetate [dihydro-linalyl acetoacetate] as a yellow oil, $n_{D}^{25} = 1.4457$; yield 362.9 g. (100.7 per cent. of theory).

d) Tetrahydro-pseudoionone.

A 1-litre 3-neck flask equipped with a stirrer, thermometer, and reflux condenser, the top of which was connected to a dry-ice trap and then to a gas meter, was charged with 362.9 g. (1.5 mols) of the 3,7-dimethyl-octen-(1)-yl-(3) acetoacetate. The flask was heated by an oil-bath to 150°—160° C., causing a rapid evolution of carbon dioxide. This had virtually ceased after about three hours, during which time the production of carbon dioxide was 92 per cent. of the theoretical. Fractional distillation of the reaction mixture from an efficient column afforded 220.8 g. of 6,10-dimethyl-undecen-(5)-one-(2) [tetrahydro-pseudoionone] (75 per cent. of theory); b.p. 72°—74° C./0.2 mm., $n_{D}^{25} = 1.4471$; $d_{4}^{25} = 0.842$.

e) Hexahydro-pseudoionone.

200 g. of the 6,10-dimethyl-undecen-(5)-one-(2) was hydrogenated, using freshly prepared 5 per cent. palladium/charcoal catalyst at 500 lbs per square inch hydrogen pressure. In one hour the temperature rose from 25° to 60° C. and the hydrogenation was completed. On fractionation, 6,10-dimethyl-undecanone-(2) [hexahydro-pseudoionone] was obtained in a fraction distilling at 68°—69° C./0.5 mm., $n_{D}^{25} = 1.433$.

What we claim is:—

1) A step in the synthesis of hexahydro-pseudoionone, which step comprises catalytically hydrogenating geranyl-acetone to hexahydro-pseudoionone.

2) A step in the synthesis of hexahydro-pseudoionone which step comprises catalytically hydrogenating tetrahydro-pseudoionone to hexahydro-pseudoionone.

3) A step in accordance with claim 1 or claim 2, wherein the catalyst used is a palladium catalyst.

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4) A synthesis of hexahydro-*pseudoionone* which comprises adding the elements of acetylene to 6-methyl-hepten-(5)-one-(2) or 6-methyl-heptanone-(2) by treating same with an alkali-metal derivative of acetylene in liquid ammonia solution and treating the product with a non-alkaline hydrolysing agent, partially hydrogenating the resulting acetylene carbinol in the presence of a palladium or nickel catalyst which selectively catalyses the reduction of a triple bond to a double bond, reacting the resulting partial hydrogenation product with diketene, eliminating the elements of carbon dioxide from the reaction product by heating same and catalytically hydrogenating the resulting geranyl-acetone or tetrahydro-*pseudoionone*.

5) A process in accordance with claim 4, wherein the partial hydrogenation is carried out in the presence of a lead-inhibited palladium/calcium-carbonate catalyst.

6) A process in accordance with claim 4 and claim 5, wherein the reaction with diketene is carried out in the presence of a weakly acid agent such as a mixture of pyridine and acetic acid or a mixture of choline and acetic acid.

7) A process in accordance with any one of claims 4 to 6 inclusive, wherein the elimination of the elements of carbon dioxide is brought about by heating the said reaction product to between 140° and 180° C.

8) A process for the manufacture of hexahydro-*pseudoionone* by the hydrogenation of geranyl-acetone or tetrahydro-*pseudoionone* and a synthesis thereof incorporating said process, substantially as described with reference to the examples given.

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